BIODEGRADABLE CUFF AN ADJUNCT TO PERIPHERAL NERVE REPAIR: A STUDY IN DOGS

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SUMMARY

This is a report of a study in which cuffs of biodegradable copolymers were placed about ulnar and peroneal nerves in legs of ten adult mongrel dogs. The results were evaluated by clinical response, electromyographic observations, nerve conduction studies, and light microscopic examination.

INTRODUCTION

For many years experimental and clinical evidence has favoured structural support about a peripheral nerve repair. (Anscombe 1970, Brady 1973). The silastic cuff has been reported (Ducker 1968) to aid longitudinal alignment of neural components, limit the gross local neuroma formation and reduce ingrowth of adjacent scar tissue at the nerve suture site. Several disadvantages have also been shown to exist following use of this non-absorbable cuff material. These include, development of neuroma proximal to the cuff, damage to nerve and adjacent tissue caused by cuff movement when placed adjacent to moving tendons or joints and finally a second surgical procedure is often necessary to remove the nondegradable cuff.

The technique of structural nerve support by cuffing would be markedly enhanced and more widely accepted if the cuff material was biodegradable, of light weight and possessing a smooth surface allowing tissue movement with little friction or trauma. Such a material has recently been demonstrated in humans and animals. The material, a copolymer of polylactic and polyglycolic acids, is a high molecular weight catabolic product of lactic acid. Properties of this material include controlled rapid degradation, (Cutright 1975, 1972, Dardik 1970, Ducker 1968), absence of toxicity, (Getter 1972, Iermann 1970, Kline 1964, Kulkarni 1966, Midgley 1968), provides a smooth lubricated surface (Miller), is easily fabricated (Morgan 1969, Kronenthal 1975), and can be altered at operation. (Kronenthal 1975, Postlethwait 1970).

METHOD AND MATERIALS

The biodegradable cuffs were custom made after determining an average size for peroneal and ulnar nerves in similar sized dogs. These cuffs were made with an inside diameter twice that of the diameter of the nerve. The cuff wall thickness was 1mm and the cuff length was 2 1/4 cm.

These cuffs were placed on peroneal and ulnar nerves in ten dogs weighing between thirty and forty pounds. One ulnar and one peroneal nerve were used for experiments and the opposite nerves were used as controls.

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The animals were anaesthetized using one (1) cc/lb methohexital sodium (Brevital Sodium). Under standard sterile operating conditions the nerves were individually approached and freed by blunt dissection. The intact nerve was elevated clear of surrounding tissue and stimulated directly with a bipolar stimulation electrode with two gold tips 10 mm apart. Duration of stimulus was 0.1 msec at sufficient amplitude to wake maximal motor response in the limb muscles. A TECA TE4 direct recording electromyograph with isolated nerve stimulator module was used. The display was recorded on direct print paper. The recording electrode was a coaxial needle placed in the appropriate muscle distal to the level of nerve section. Ground electrodes were placed between stimulating and recording electrodes. Motor latency times were determined for each individual nerve at the time of surgery prior to nerve section and repair. These studies were repeated for each nerve at the time of harvest in order to document motor recovery. Also at time of harvest electromyograph examination of appropriate limb muscles was done using concentric needle electrodes.

The surgery and nerve repair was performed using magnification and interrupted 9-0 nylon epineural sutures.

The nerve samples were harvested on a schedule varying from eight to twenty-four weeks postoperatively.

All animals were observed daily. All were active and had gained weight at the time of nerve harvesting.

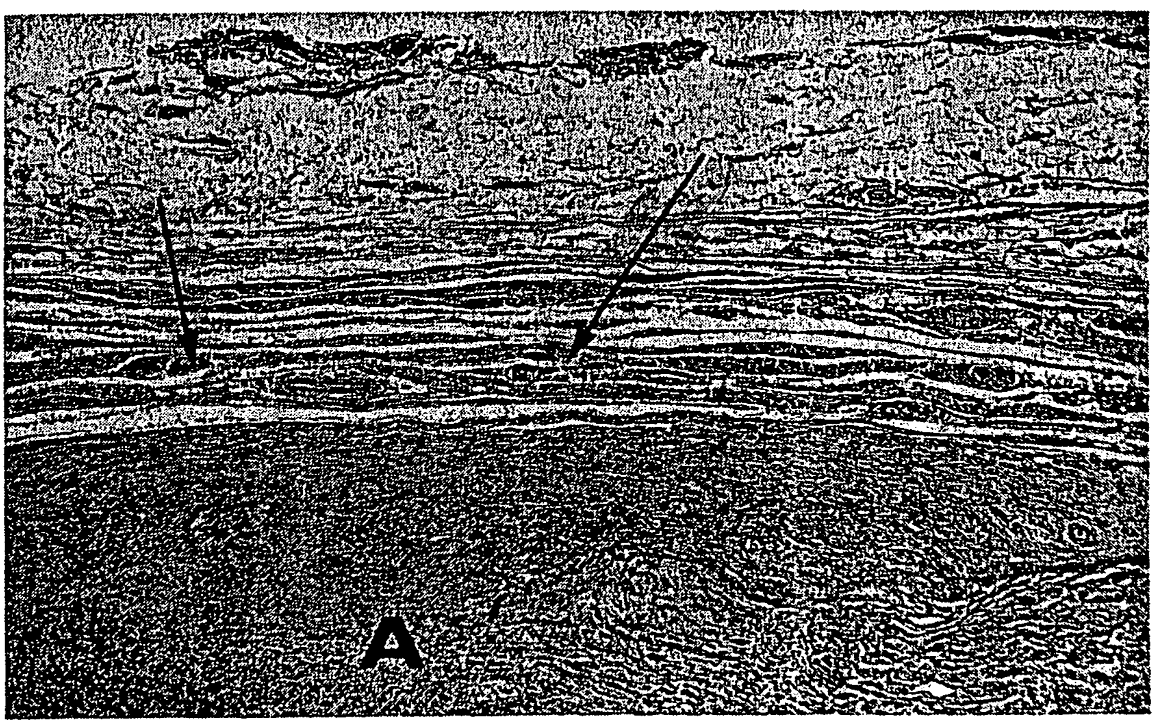

Fig. 1. Eight week sample of the biodegradation of a copolymer nerve cuff.
The biodegradation can be seen as a line of copolymer particles and phagocytic cells (arrows) separating the nerve from the outer connective tissue. The suture line is at lower left (A). X 40.

RESULTS

Tissue Reaction to the Cuff

The early reaction to the biodegradable copolymer has been discussed in several papers, (Ducker 1968, Miller, Morgan 1969, Postlethwait 1970). The reaction has been generally one of hydrolysis and phagocytosis with occasional giant cells and with few typical inflammatory cells such as polymorphonuclear leucocytes, plasma cells and lymphocytes.

The reaction in this experiment was similar to that referred to above. The eight week samples showed partial breakdown of the cuff into small particles. These particles were surrounded by many phagocytic cells which dispersed slowly as the material hydrolyzed and disappeared in the later time samples. Figs. 1-4 show the breakdown sequence from eight to twelve weeks. The final degradation (disappearance) varied over a period of three weeks when all samples were considered. However, by eight weeks it was essentially degraded to where tissue proliferated through it and it no longer served as a barrier to the ingrowth of perineural connective tissue (Fig. 1).

The proliferation of fibrous connective tissue between the nerve and the inside of the cuff was in a parallel fashion as shown in Figs. 1 and 2. This connective tissue was most likely epineural in origin and had not proliferated from perineural sources outside the cuff.

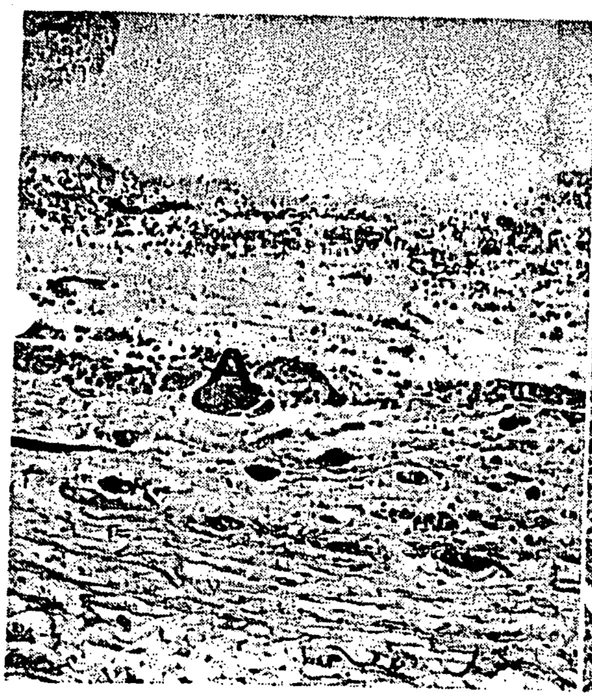

Fig. 2. Ten week sample of the degradation process.
One particle of copolymer remains (A) phagocytes loaded with the final residue of the material can be seen as a line which the copolymer formerly occupied. Tissue reaction is minimal. X 130.

Fig. 3. Eleven week samples.
Only a line of phagocytic cells remain. (arrow) tissue reaction minimal. X 52.

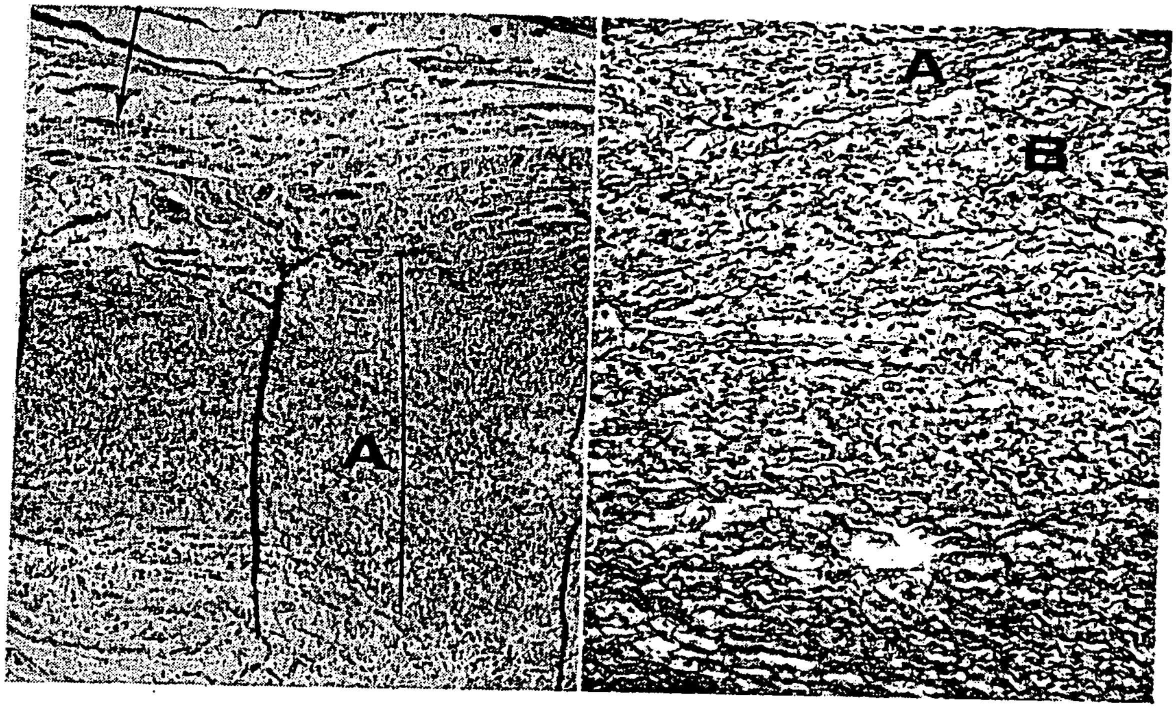

Fig. 4. Twelve week sample.
The last evidence of copolymer found in the total study is shown as a line of phagocytic cells (arrow). The connective tissue between nerve A and the phagocytic cells shows little evidence of scarring. X 50.

Fig. 5. Nerve alignment at the site of repair at eight weeks.
The individual nerves are mostly parallel with only occasional nerves growing in an undirected manner A & B. X 130.

The distance of the nerve itself from the area of degradation of the copolymer in most cases appeared to be greater than necessary for optimum nerve repair or indeed to prevent an overgrowth of connective tissue around the nerve inside the cuff (Figs. 1-4).

The nerve alignment in both control nerves and experimental nerves was inconstant. Three experimental junctional sites are shown in Figs. 5, 6, 7. The alignment in Fig. 6 at eight weeks appears excellent while in Fig. 8 at ten weeks the alignment of the individual nerve fibres was less parallel. Fig. 7 at nine weeks shows considerable overlapping and loss of typical parallel arrangement. However, evidence of post-traumatic neuroma formation is not present.

Nerve Conduction

The nerve conduction studies first showed evidence of motor return in both the test and control nerves at approximately the ninth week after section and repair. In subsequent weeks there was a tendency for the motor latency time to decrease and for the compound muscle action potential to increase in amplitude and decrease in temporal dispersion. There was a wide variation in the postoperative response from animal to animal. Because of the small number of animals no statistical significance could be placed on the results. Also no statistical significance could be documented between the test and control nerves.

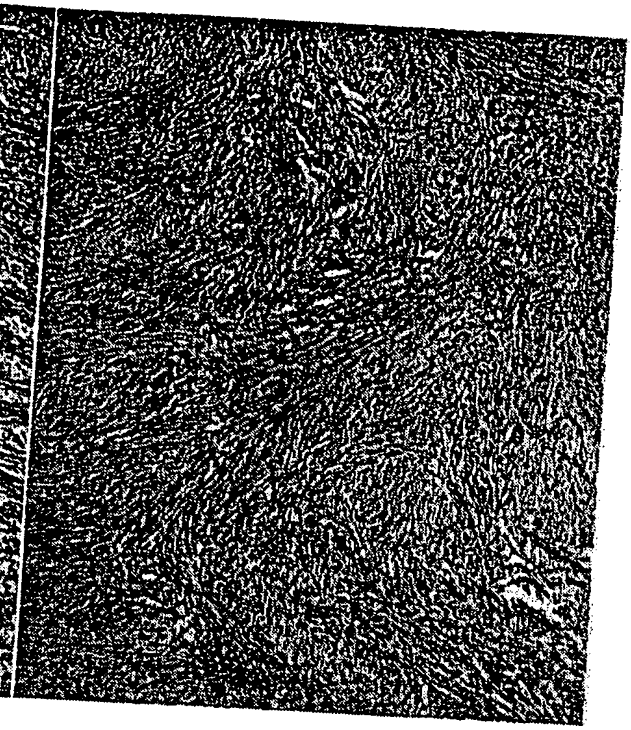

Fig. 6. Nerve alignment shown at ten weeks.
It is evident throughout this site of repair that nerve regeneration is haphazard and overlapping. X 64.

Fig. 7. Nerve alignment shown at nine weeks.
This repair site shows poor directional growth. X 64.

Electromyography of the appropriate muscles revealed positive sharp waves and fibrillation potentials from the eighth through the twenty-fourth postoperative weeks. The positive sharp waves and fibrillations decreased in quantity after the sixteenth week. Again, no definite difference could be documented between the test nerves and the controls.

Histopathological Examination

Each nerve (control and experimental) was affixed to white cardboard, the distal and proximal ends were marked and then the cardboard and nerve were placed in 10% buffered formalin. The nerves were examined grossly by bisecting as near as possible through the centre of the longitudinal axis of the nerve and repair site. This was not always possible. Both halves of the nerves were oriented and embedded in paraffin, sectioned at 4 microns and stained with Haematoxylin and eosin, Masson's trichrome and Bodians. The slides were examined and recuts ordered where the repair site was not properly bisected. A minimum of eight slides were microscopically analyzed for each of the following:

a. nerve fibre alignment at junctional site judged on a one to three basis. A one(1) representing good alignment and a three(3) representing poor alignment.

b. thickness of fibrotic reaction around the nerve at the junctional site measured in microns.

c. width of nerve repair proper at the junctional site measured in microns.

d. noting if sutures present insuring sections were from junctional site.

All slides were read blind. The pathologist having never known which were controls and which experimental. All measurements were taken with a Filar Micrometer attachment, calibrated to each lens utilized.

Nerve alignment: Eighteen experimental and eighteen control peroneal nerves allowed for an analysis of alignment as previously described. When the total analysis figures for each nerve were added and an average determined the controls and experimental average numbers were identical. The ulnar nerve was suitable for analysis in twenty experimental samples and in eighteen control samples. Again when an average number was determined they were identical (see Table I).

TABLE I
HISTOPATHOLOGICAL ANALYSIS

	Number of Junctional sites Analyzed	*Alignment*	*Fibrosis*	*Width of Nerve Repair*
	Figures are Averages			
Peroneal Experimental	18	2.2	510 microns	1410 microns
Peroneal Control	18	2.2	714 microns	2287 microns
Ulnar Experimental	20	2	886 microns	2548 microns
Ulnar Controls	18	2	1043 microns	3000 microns

Fibrosis: The amount of fibrosis around the junctional sites was assessed and averaged. In both nerves the experimental junctional sites were judged to have more fibrosis than the corresponding control sites. Similarly eight control sites showed more fibrosis than the corresponding experimental sites (see Table 1).

Width or nerve repair: The nerve measurements were done by microscopically selecting the best cross section of nerve and then measuring, at the site of junction, the fibrous connective tissue thickness outside the nerve itself. Although not a highly reliable procedure, when done uniformly throughout the slide analysis, the experimental nerves scored lower than the controls in both nerves indicating less fibrosis (Table 1).

Histology: In thirty-six nerves studied the pathologist was able to find evidence of the perineural sutures in thirty cases. Thus indicating the exact site of junction. In three additional samples the site of junction was identified. In the other three it was difficult to determine if indeed the junctional site was exactly identified.

DISCUSSION

The biodegradable cuffs were easily utilized with standard operating armamentarium. The tissue reaction to the cuffs throughout was minimal. The average fibrosis measurement was uniformly lower in the experimental nerves. This indicates that the use of the cuff is advantageous and decreases fibrosis and scarring.

No difference in alignment was found between the experimental and control nerves.

The cuffs were essentially degraded by eight weeks at which time they no longer acted as a barrier to the ingrowth of fibrous connective tissue. Some samples showed a thin line of phagocytic cells at twelve weeks as the last evidence of the copolymer.

Size of the cuff: Ducker and Hayes (1968) state in the dog that the maximum direct axonal spanning of the laceration site without connective tissues or neuroma build up was achieved utilizing tubes whose internal cross-section was twice that of the nerve. In this study an attempt was made to achieve a similar relationship but many of the tissue sections revealed a build up of connective tissue running parallel to the nerve and located between the cuff and the epineurium. The authors question if this relationship is entirely appropriate and if it could be partially prevented with smaller inside diameter cuffs. Some of our earlier work confirms that when the cuff is snugly applied to the suture site a neuroma develops just proximal to the cuff before biodegradation of the cuff material has occurred. It is obvious that the cuff-nerve diameter relationship is critical and from a practical, clinical point of view difficult to achieve.

Conduction studies: The authors were unsuccessful in showing any statistical difference electrically between the cuffed versus standard nerve repairs. The equipment either failed in its degree of sophistication to show any difference or the sample was too small or there is no change in the results with the addition of the cuff to the nerve repair.

CONCLUSIONS

This study on repair of peripheral nerves has demonstrated the following:

a. the biodegradable cuff is readily placed with conventional surgical armamentarium.

b. tissue tolerance to the cuff is high.

c. Fibrosis around the nerve is less with use of the cuff.

d. Exact microscopic nerve alignment is difficult to achieve even with magnifica-.ion.

e. No increase in conductivity could be demonstrated utilizing the cuff. Refined nerve conduction techniques may help differentiate the experimental versus the control nerve.

f. The inside cuff diameter to nerve diameter does not appear to be optimally 2 to 1 utilizing these biodegradable cuffs.

g. The development of better methods of evaluating peripheral nerve reponses is needed.

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In conducting the research described in this report the investigators adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the committee on the Guide for Laboratory Animals Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences – National Research Council.

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